AMENDMENT TO THE SPECIFICATION

In the Specification:

Please insert the Sequence Listing consisting of 22 sheets, provided herewith, into the application. The Sequence Listing is provided, as required, to comply with the requirements of 37 C.F.R. § 1.821 through 1.825. I hereby submit that the Sequence Listing contains no new matter.

Please replace the paragraph on page 4, line 3 through page 5, line 8 of the specification with the following paragraph:

> In the first aspect, the invention provides purified wild-type mammalian methionine synthase gene, and mutated and polymorphic versions of the mammalian methionine synthase gene, fragments of the wild-type, mutated, and polymorphic gene, and sense and antisense sequences which may be used in the methods of the invention. Preferably, the gene is human. The proteins encoded therefrom are also an aspect of the invention as is a methionine synthase polypeptide having conservative substitutions. Preferably, the protein is a recombinant or purified protein having a mutation conferring hyperhomocysteinemia when present in a mammal. In addition, nucleic acids, including genomic DNA, mRNA, and cDNA, and the nucleic acid set forth in SEQ ID NO: 1, or degenerate variants thereof, are provided. The shorter nucleic acid sequences are appropriate for use in cloning, characterizing mutations, the construction of mutations, and creating deletions. In one embodiment, the nucleic acid set forth in SEQ ID NO: 1 is a probe that hybridizes at high stringency to sequences found within the nucleic acid of SEQ ID NO: 1. In further embodiments, the probe has a sequence complementary to at least 50% of at least 60 nucleotides, or the sequence is complementary to at least 90% of at least 18 nucleotides. Protein fragments also are provided. The shorter peptides may be used, for example, in the generation of antibodies to the methionine synthase protein. In some embodiments of this aspect of the invention nucleic acid fragments useful for detection of mutations in the region of the methionine synthase gene which encodes the cobalamin

binding domain, and for detecting those mutations which indicate an increased likelihood of hyperhomocysteinemia, are preferred. Most preferred fragments are those useful for detecting the 2756 A G, bp 2640-2642, and 2758 C G mutations/polymorphisms. Given Applicants' discovery, one skilled in the art may readily determine which nucleic acids, detection methods, and mutations are most useful. Mutant proteins encoded by these mutations, including, but not limited to, H920D, Ile 881, and D919G are also provided by the invention (see, for example SEQ ID NOs: 74 and 75). Such mutant and polymorphic polypeptides may have decreased or increased biological activity, relative to wild-type methionine synthase.

Please replace the paragraph on page 21, lines 1-8, of the specification with the following paragraph:

Fig. 1 is a diagram showing four homologous regions among methionine synthases. Boxes 1 to 4 were used to design degenerate oligonucleotides for the initial cloning experiments. Ec: *Escherichia coli*, accession number J04975 (SEQ ID NOs: 3, 9, 15, and 21); Ss: *Synechocystis sp.*, accession number D64002 (SEQ ID NOs: 4, 10, 16, and 22); Ml1 and Ml2: *Mycobacterium leprae*, accession number U000175 (see Drennan *et al.*, 1994; SEQ ID NOs: 5, 11, 17, and 23); Hi: *Haemophilus influenzae*, accession number U32730 (SEQ ID NOs: 6, 12, and 18); Ce: *Caenorhabditis elegans*, accession number Z46828 (SEQ ID NOs: 7, 13, 19, and 24); Hs: *Homo sapiens*, this work (SEQ ID NOs: 8, 14, 20, and 25). Identical residues are indicated by a star above the alignment. Amino acid position for each protein is shown at left.

Please replace the paragraph on page 22, lines 9-17, of the specification with the following paragraph:

Fig 6. shows an amino acid sequence comparison among methionine synthases in the Box 2 region. Identical residues are indicated by a star above the alignment. Dots show partially conserved residues, for which at least 6/7 identical or similar residues can be aligned (A,G,S,T; D,E,N,Q; V,L,I,M; K,R; and F,W,Y (Bordo,D. and Argos,P. (1991) *J. Molec. Biol.*, **217**, 721-729)). Mutations identified in this work are shown below the

alignment. For abbreviations, see Fig.1; Mm: *Mus musculus* (SEQ ID NOs: 67-73). The seven amino acids conserved in cobalamin-binding proteins (Drennan, C.L., Huang, S., Drummond, J.T., Matthews, R.G., and Ludwig, M.L. (1994) *Science*, **266**, 1669-1674) are underlined.

Please replace the paragraph on page 34, lines 12-22, of the specification with the following paragraph:

The coding sequence of human methionine synthase contains 3795 bp (SEQ ID NO:1) encoding a polypeptide of 1265 amino acids in length (SEQ ID NO:2) (Fig. 3), exceeding the length of published methionine synthases by 11-29 residues. The putative initiation codon is in a sequence of good context for the initiation of translation in eukaryotic cells (GACAACATGT, underlined nucleotides matching Kozak consensus (SEQ ID NO: 76; Kozak,M. (1991) *J. Biol. Chem.*, **266**, 19867-19870)). The predicted MW of methionine synthase is 141,000, comparing favorably with the published size of 151,000 based on SDS-polyacrylamide electrophoresis of the pig enzyme (Chen, Z., Crippen, K., Gulati, S., and Banerjee, R. (1994) *J. Biol. Chem.*, **269**, 27193-27197). It shares 58% identity with the *E. coli* and 65% identity with the *C. elegans* enzyme.

CONCLUSION

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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